Biological Psychiatry

Translating Oxytocin Neuroscience to the Clinic: A National Institute of Mental Health Perspective

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Oxytocin and the closely related nine-amino acid neuropeptide vasopressin have long been trendsetters. At the beginning of the 20th century, they defined the neurohypophysis; midway through the century, they demonstrated the importance of disulfide bonds for neuropeptide structure and function (leading to the 1955 Nobel Prize in Chemistry); and over the last few decades, they have become the darlings of behavioral neuroscientists because of their central role in learning, stress, and social behavior. In the past decade, oxytocin has moved into the world of clinical neuroscience. At the end of 2014, a search of "oxytocin and intranasal" revealed 99 trials listed in ClinicalTrials.gov with 253 citations in PubMed since 2009.

The allure of oxytocin stems partly from a body of work showing that the peptide is necessary and sufficient for many aspects of social behavior, from maternal care to pair bonding, in experimental animals (1). These studies were feasible because in these species the peptide could be administered directly into the brain, and access to specific and potent antagonists allowed careful pharmacologic study of local effects. The advent of transgenic mice with constitutive or conditional knockout of oxytocin or its receptor helped to refine the peptide's role in maternal care and social cognition. More recently, using conditional, region-specific knockouts of the oxytocin receptor, a specific class of cells in the mouse prefrontal cortex has been shown to be a target for oxytocin's effect on sociosexual behavior (2).

Beyond the specifics of this exciting and growing literature, these studies suggest three general concepts that can guide us as we consider translation from bench to bedside. Given the enthusiasm for clinical trials with intranasal oxytocin, these concepts may be helpful in managing expectations.

Concepts to Guide Translation from Bench to Bedside

First, sex matters. The canonical functions of oxytocin for parturition and lactation are female-specific and steroid-dependent. Although it is possible that effects in the central nervous system are less sex-specific and less steroid-dependent, that has not been the rule in rodent studies. The central release of oxytocin and the expression of the oxytocin receptor in brain have been shown to be influenced by estrogen, just as the expression of vasopressin has been the classic example of an androgen-dependent system in the brain (3). Human neuroimaging studies after administration of intranasal oxytocin show sex-dependent effects (4).

Second, species matters. Oxytocin is necessary and sufficient for attachment behavior in prairie voles but has no such effects in meadow voles. Comparative studies demonstrate substantial differences in the behavioral and cognitive roles of oxytocin going from voles to mice to rats, largely secondary to the species-typical patterns of receptor expression (5). Although oxytocin cells are largely limited to the paraventricular and supraoptic nuclei of the hypothalamus across mammals, the variation in receptor expression is profound. Species with high levels of oxytocin receptors in brain regions associated with reward tend to show high levels of affiliative behavior. We know this is more than a correlation because viral vector–mediated changes in local receptor expression lead to predictable changes in social behavior (5). Oxytocin receptors have been difficult to detect in the human brain, although the receptor has been mapped in macaques where expression is high in cholinergic regions of the forebrain (6).

Third, chemistry matters. Neuropeptides are not good drugs. They have limited bioavailability by oral administration, are metabolized quickly in the circulation, and achieve limited access to brain receptors. Intravenous oxytocin with a plasma half-life of about 3 minutes is effective for inducing uterine contraction but not as a central agent. Intranasal administration improves central bioavailability, but dose is difficult to regulate or replicate via this route (7). With opiates, access to a nonpeptide agonist-like morphine has allowed rigorous investigation in humans and experimental animals. However, with oxytocin, developing a nonpeptide agonist has proven challenging, with compounds that are selective for the oxytocin receptor in one species appearing selective for the V1a receptor in another. WAY-267464 was developed as a selective, nonpeptide agonist with good brain penetration for oxytocin receptors (8), but more recent data have called its selectivity into question (9), and selectivity in humans has yet to be demonstrated.

New Requirements for Clinical Trials

These three principles suggest some of the challenges of translational research in this area. Translational research for neuropeptides in general has been a story of unfulfilled promises. The hopes from robust effects with agents affecting corticotropin-releasing factor receptors, substance P receptors, and vasopressin receptors in rodents have not translated to medications for brain disorders in humans. Could the story have a happier ending for oxytocin? Does the evidence in humans showing effects on social cognition demonstrate that clinical efficacy is around the corner? Specifically, given that oxytocin appears to have prosocial effects, will the neuropeptide improve social cognition in patients with schizophrenia or social motivation in patients with autism?

The answers to these questions reside ultimately in empirical studies. From the perspective of the National Institute of Mental Health (NIMH), rigorous clinical trials with oxytocin will not be easy. The NIMH no longer accepts unsolicited trials. To

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improve the rigor and reproducibility of clinical trials, each study must demonstrate target engagement, which means evidence of activation of a proposed mechanism at a clinically effective dose. Occupancy of oxytocin receptors in a specific brain area would be an excellent example of target engagement, but so far there is no positron emission tomography ligand and no compelling evidence of oxytocin receptors in the human brain. Changes in local neurophysiology or regional brain activity might be evidence of oxytocin's central effects, even without receptor binding studies. However, to demonstrate target engagement, it would not be sufficient to measure such changes before and after treatment. The protocol would need to show a range of doses with target engagement defining the effective dose.

Why is the NIMH so demanding about target engagement? Ideally, clinical trials should be equally informative with either positive or negative effects of the intervention. If the compound lacks efficacy, without a measure of target engagement, there is no way to distinguish insufficient dose from insufficient efficacy. As a result, most negative trials fail to falsify a hypothesis, are not informative, and never get published. The implicit bias toward positive results leads to reports of efficacy that frequently are not replicable in phase 3 trials (10). Even with positive outcomes, the effective dose may not be clearly defined. Dose may be especially difficult to control with intranasal administration, so these issues are more germane for oxytocin, where randomized, double-blind trials are giving very mixed results for schizophrenia and autism (see other articles in this issue).

Beyond asking what we will learn from a negative trial, the NIMH asks what will we gain from a positive trial? The NIMH clinical portfolio is not funded only to support publications. In this area, we need to see a pathway to a product that can be developed. Here the questions are especially difficult: Who would develop the treatment for clinical use, what are the regulatory barriers, and how would the indications for using oxytocin as a treatment be best defined? The NIMH has little influence over the first two questions, but these need to be considered carefully early in the process.

The indications question is very much relevant to NIMH. As we move away from a narrow focus on categorical diagnosis, the NIMH is looking for interventions that influence domains of function. Social cognition is an especially intriguing opportunity, but the community needs to be careful to define common approaches to assessing social cognition that can be used across ages, disorders, and cultural/ethnic groups. A scan of the effects of intranasal oxytocin in healthy volunteers includes trust, social reciprocity, eye contact, and social memory. In assessments of social cognition, the details matter. Because different aspects of social cognition are affected in schizophrenia, autism, and mood disorders, careful thought needs to be given to the details of the cognitive process that one plans to influence with oxytocin. In addition to dose, factors such as sex and age may be critical.

In conclusion, it is entirely predictable that the studies demonstrating prosocial effects of oxytocin in rodents would encourage the use of oxytocin to treat social deficits in humans. However, the studies in rodents demonstrate that oxytocin effects are species-specific. The mechanism for these species differences is the remarkable species differences in the regional expression of brain oxytocin receptors. Without a clear picture of the landscape of oxytocin receptors in the human brain, clinical studies cannot be linked rigorously to preclinical research. A considerable literature describes effects of intranasal oxytocin on social cognition in humans. Before this literature can be translated into clinical trials for patients with social deficits, we need to know the target of intranasal oxytocin and carefully consider the dosage needed for target engagement. In the absence of dose effects with target engagement, negative results would not be interpretable, and positive results may not be reproducible. A safe, effective prosocial compound could have high value for people with social deficits. Although there has been great hope that intranasal oxytocin could be the answer, a nonpeptide agonist might ultimately offer greater efficacy.

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Article Information

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